L2 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:527656 BIOSIS
DOCUMENT NUMBER: PREV200000527656
TITLE: A novel gene discovered by Methylation Sensitive-Representational Difference Analysis (MS-RDA) is involved in multidrug resistance.
AUTHOR(S): Shan, Jidong (1); Yuan, Liming (1); Budman, Daniel (1); Allen, Steve (1); Chiorazzi, Nicholas (1); Vinciguerra, Vincent (1); Xu, Hao-peng (1)
CORPORATE SOURCE: (1) Molecular Oncology, Hematology/Oncology Medicine, Rheumatology/Clinical Immunology, North Shore-Long Island Jewish Health System, New York University School of Medicine, New York, NY USA
SOURCE: International Journal of Molecular Medicine, (2000) Vol. 6,

No. Supplement 1, pp. S20. print.
Meeting Info.: Joint Meeting of the 5th World Congress on Advances in Oncology and the 3rd International Symposium on

Molecular Medicine Crete, Greece October 19-21, 2000
ISSN: 1107-3756.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L8 ANSWER 21 OF 41 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 94296567 MEDLINE
DOCUMENT NUMBER: 94296567
TITLE: Identification of two nuclear protein binding sites and their role in the regulation of the murine multidrug resistance mdr1a promoter.
AUTHOR: Cohen D; Yu L; Rzepka R; Horwitz S B
CORPORATE SOURCE: Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461..
CONTRACT NUMBER: CA 39821 (NCI)
5P30CA13330 (NCI)
SOURCE: DNA AND CELL BIOLOGY, **(1994 Jun)** 13 (6) 641-9.
Journal code: AF9. ISSN: 1044-5498.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410

AB **Multidrug resistance** genes (mdr) that encode P-glycoproteins (P-gp) are transcriptionally regulated in normal tissues and in some multidrug-resistant (MDR) cells. Several lines of evidence suggest that regulation of P-gp overexpression at the transcriptional level is also important in human tumors. In murine MDR cells, mdr1a and/or mdr1b genes are overexpressed and P-gp isoforms are overproduced. To identify the mdr1a promoter regions that are required for transcription, the promoter has been linked to the chloramphenicol acetyltransferase (CAT) gene in transient expression vectors. 5'-Deletions of the promoter sequences have demonstrated that the region between -155 to +89 bp is crucial for basal activity of the mdr1a gene. DNase I footprinting, **methylation** interference, and gel retardation assays identified two nuclear protein binding sites within these sequences. One of the nuclear protein binding sites contains an 11-bp DNA sequence that interacts with nuclear protein(s) and is conserved in the promoters of the murine mdr1a and mdr1b, hamster pgp1, and human MDR1 genes. The conserved SP1 site (5'-GGGCGGG-3') that is present further downstream was shown to interact with its nuclear factor. These observations suggest that at least part of mdr gene transcriptional regulation is mediated by conserved mdr cis-regulatory elements and common nuclear factors.

L8 ANSWER 41 OF 41 MEDLINE DUPLICATE 28

ACCESSION NUMBER: 72094293 MEDLINE

DOCUMENT NUMBER: 72094293

TITLE: **Methylation** of cytosine residues in DNA controlled by a **drug resistance** factor (host-induced modification-R factors-N 6 -methyladenine-5-methylcytosine).

AUTHOR: Hattman S; Gold E; Plotnik A

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1972 Jan)** 69 (1) 187-90.
Journal code: PV3. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 197205

L8 ANSWER 32 OF 41 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 89324234 MEDLINE
DOCUMENT NUMBER: 89324234
TITLE: Pharmacodynamic and DNA methylation studies of high-dose 1-beta-D-arabinofuranosyl cytosine before and after in vivo 5-azacytidine treatment in pediatric patients with refractory acute lymphocytic leukemia.
AUTHOR: Avramis V I; Mecum R A; Nyce J; Steele D A; Holcenberg J S
CORPORATE SOURCE: Department of Pediatrics, School of Medicine, University of Southern California, Childrens Hospital of Los Angeles 90027.
CONTRACT NUMBER: CA 38905 (NCI)
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, **(1989)** 24 (4) 203-10.
Journal code: C9S. ISSN: 0344-5704.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198911

AB The primary development of clinical resistance to 1-beta-D-arabinofuranosyl cytosine (ara-C) in leukemic blast cells is expressed as decreased cellular concentrations of its active anabolite. Correlations exist between the cellular concentrations of 1-beta-D-arabinofuranosyl cytosine 5'-triphosphate (ara-CTP) in leukemic blast cells and inhibition of DNA synthetic capacity with the clinical response to high-dose cytosine arabinoside (HDara-C). 5-Azacytidine (5-Aza-C) and its congeners are potent DNA hypomethylating agents, an action closely associated with the reexpression of certain genes such as that for deoxycytidine kinase (dCk) in ara-C-resistant mouse and human leukemic cells. Reexpression of dCk could increase the cellular ara-CTP concentrations and the sensitivity to ara-C. A total of 17 pediatric patients with refractory acute lymphocytic leukemia (ALL) received a continuous infusion of 5-Aza-C at 150 mg/m2 daily for 5 days after not responding to (13/17) or relapsing from (4/17) an HDara-C regimen (3 g/m2 over 3 h, every 12 h, x 8 doses). Approximately 3 days after the end of the 5-Aza-C infusion, the HDara-C regimen was given again with the idea that the induced DNA hypomethylation in the leukemic cells may have increased the dCk activity and that a reversal of the tumor **drug resistance** to ara-C could have occurred. Deoxycytidine kinase (expressed as cellular ara-CTP concentrations) in untreated blasts, DNA synthetic capacity (DSC), and the percentage of DNA methylcytidine levels were determined before and after 5-Aza-C administration. Cellular ara-CTP was enhanced to varying degrees in 15 of 16 patients after 5-Aza-C treatment. The average cellular concentration of ara-CTP determined in vitro by the sensitivity test was 314 +/- 390 microM, 2.3-fold higher than the average value before 5-Aza-C treatment. In 12 patients in whom the DNA **methylation** studies were completed before and after 5-Aza-C treatment, the average DNA hypomethylation level was 55.6% + 15.8% of pretreatment values (n = 13; mean +/- SD). DSC showed a profound decline in 2/9 evaluable patients who achieved a complete response (CR) after this regimen. The data suggest that treatment with a cytostatic but DNA-modulatory regimen of 5-Aza-C causes DNA hypomethylation in vivo, which is associated with dCk

reexpression in the patients' leukemic blasts. The partial reversal of **drug resistance** to ara-C by 5-Aza-C yielded two CRs in this poor-prognosis, multiply relapsed patient population with refractory ALL.(ABSTRACT TRUNCATED AT 400 WORDS)

L8 ANSWER 29 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:106734 BIOSIS
DOCUMENT NUMBER: BR42:46734
TITLE: DRUG SYNERGISM ANTAGONISM AND COLLATERAL SENSITIVITY INVOLVING GENETIC CHANGES.
AUTHOR(S): AVRAMIS V I; HUANG S-H; HOLCENBERG J S
CORPORATE SOURCE: DIV. HEMATOLOGY ONCOLOGY, CHILDRENS HOSP. LOS ANGELES, LOS ANGLES, CALIF. 90054.
SOURCE: CHOU, T.-C. AND D. C. RIDEOUT (ED.). SYNERGISM AND ANTAGONISM IN CHEMOTHERAPY. XVI+752P. ACADEMIC PRESS, INC.:
SAN DIEGO, CALIFORNIA, USA; LONDON, ENGLAND, UK. ILLUS, (1991) 0 (0), 585-620.
ISBN: 0-12-174090-0.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L13 ANSWER 11 OF 53 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 97267787 MEDLINE
DOCUMENT NUMBER: 97267787 PubMed ID: 9113116
TITLE: Drug-induced DNA **hypermethylation**: a potential mediator of acquired **drug resistance** during cancer chemotherapy.
COMMENT: Comment in: Mutat Res. 1997 Apr;386(2):103-5
AUTHOR: Nyce J W
CORPORATE SOURCE: Department of Molecular Pharmacology and Therapeutics, EpiGenesis Pharmaceuticals, Greenville, NC 27858, USA.
CONTRACT NUMBER: CA RO1 47217 (NCI)
SOURCE: MUTATION RESEARCH, **(1997 Apr)** 386 (2) 153-61.
Ref: 60
Journal code: NNA; 0400763. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970523
Last Updated on STN: 19980206
Entered Medline: 19970512

L13 ANSWER 12 OF 53 CANCERLIT

ordered

46 ANSWER 7 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:421273 BIOSIS
DOCUMENT NUMBER: PREV199799720476
TITLE: Isolation of novel cDNAs **differentially expressed** in **MCF**-7 and MCF-10 breast cell lines.
AUTHOR(S): Sturges, Michael R.; Little, Brian M.; Kounine, Melissa; Passavant, C. W.
CORPORATE SOURCE: Cascade Oncogenics Inc., Portland, OR 97201 USA
SOURCE: FASEB Journal, (1997) Vol. 11, No. 9, pp. A1201.
Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L46 ANSWER 4 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998155625 MEDLINE
DOCUMENT NUMBER: 98155625 PubMed ID: 9494521
TITLE: Assignment of the human progression associated protein (PAP) to chromosome 12p12.3.
AUTHOR: Schiemann S; Valentine M; Weidle U H
CORPORATE SOURCE: Boehringer Mannheim GmbH, Penzberg, Germany.
SOURCE: ANTICANCER RESEARCH, **(1997 Nov-Dec)** 17 (6D) 4281-5.
Journal code: 59L; 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 19980407
Entered Medline: 19980326

AB Analysis of mammary carcinoma cell lines **MCF-7** and MCF-7ADR by **differential display** resulted in the identification of a new putative transmembrane protein, PAP (Progression Associated Protein). Cell lines MCF-7 and MCF-7ADR represent a model system for the identification of genes involved in the clinical progression of human breast cancer. According to the functions assigned to some members of its family, PAP might be involved in cell cycle regulation and cell-cell interactions. Here we describe the chromosomal localization of the PAP gene by the use of fluorescence in situ hybridization (FISH) with two different genomic DNA probes, derived from the 3'-untranslated and the 5'-translated region of the PAP cDNA sequence. The results of the chromosomal localization experiments indicate that the PAP gene is located on human chromosome 12p12.3.

L18 ANSWER 7 OF 12 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 91371346 MEDLINE
DOCUMENT NUMBER: 91371346 PubMed ID: 1680024
TITLE: Subcellular distribution of daunorubicin in P-glycoprotein-positive and -negative drug-resistant cell lines using laser-assisted confocal microscopy.
AUTHOR: Gervasoni J E Jr; Fields S Z; Krishna S; Baker M A; Rosado M; Thuraisamy K; Hindenburg A A; Taub R N
CORPORATE SOURCE: Department of Medicine, Columbia University, New York, New York 10032.
CONTRACT NUMBER: CA-31761 (NCI)
CA-40188 (NCI)
CA-42450 (NCI)
SOURCE: CANCER RESEARCH, **(1991 Sep 15)** 51 (18) 4955-63.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911108
Last Updated on STN: 19970203
Entered Medline: 19911021

AB Four well defined multidrug-resistant cell lines and their drug-sensitive counterparts were examined for intracellular distribution of **daunorubicin** (DNR) by laser-assisted confocal fluorescence microscopy: P-glycoprotein-negative HL-60/AR cells, and P-glycoprotein-positive P388/**ADR**, KBV-1, and MCF-7/**ADR** cells. Both drug sensitive cell lines (HL-60/S, P388/S, KB3-1, and MCF-7/S) and drug-resistant cell lines (HL-60/AR, P388/**ADR**, KBV-1, and MCF-7/**ADR**) exposed to DNR showed a similar rapid distribution of drug from the plasma membrane to the perinuclear region within the first 2 min. From 2-10 min, the drug sensitive HL-60/S, P388/S, and MCF-7/S cells redistributed drug to the nucleus and to the cytoplasm in a diffuse pattern. In contrast, drug-resistant HL-60/AR, P388/**ADR**, and MCF-7/**ADR** redistributed DNR from the perinuclear region into vesicles distinct from nuclear structures, thereby assuming a "punctate" pattern. This latter redistribution could be inhibited by glucose deprivation (indicating energy dependence), or by lowering the temperature of the medium below 18 degrees C. The differences in distribution between sensitive and resistant cells did not appear to be a function of intracellular DNR content, nor the result of drug cytotoxicity. Drug-sensitive KB3-1 and -resistant KBV-1 cells did not fully follow this pattern in that they demonstrated an intracellular DNR distribution intermediate between HL-60/S and HL-60/AR cells with both "punctate" and nuclear/cytoplasmic uptake sometimes in the same cell. These data indicate that the intracellular distribution of DNR is an important determinant of drug resistance regardless of the overexpression of P-glycoprotein. The intracellular movement of drug requires the presence of glucose and a temperature above 18 degrees C, implicating energy-dependent processes and vesicle fusion in the distribution process. This **intracellular transport** of DNR away from the nucleus in multidrug-resistant cells may protect putative cell targets such as DNA against drug toxicity.

L36 ANSWER 29 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 94:693742 SCISEARCH
THE GENUINE ARTICLE: PP021
TITLE: EXPRESSION OF THE MULTIDRUG-RESISTANCE ASSOCIATED PROTEIN AND P-GLYCOPROTEIN IN DOXORUBICIN-SELECTED HUMAN MYELOID-LEUKEMIA CELLS
AUTHOR: SLAPAK C A (Reprint); MIZUNUMA N; KUFE D W
CORPORATE SOURCE: HARVARD UNIV, SCH MED, DANA FARBER CANC INST, DIV CANC PHARMACOL, 44 BINNEY ST, NO D1730, BOSTON, MA, 02115 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: BLOOD, (**01 NOV 1994**) Vol. 84, No. 9, pp. 3113-3121.
ISSN: 0006-4971.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 65

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Drug-resistant sublines of the human U-937 myeloid leukemia cell line were selected in doxorubicin concentrations of 10, 40, and 200 ng/mL (designated U-A10, U-A40, and U-A200, respectively). Northern blot analysis showed overexpression of the multidrug resistance-associated protein (MRP) **gene**, but not MDR1, in U-A10 cells as compared with parental U-937 eels. Prolonged passage of U-A10 cells in 10 ng/mL of doxorubicin had little effect on MRP RNA levels, but increased MDR1 expression. The U-A40 and U-A200 cells, derived by selection of U-A10 cells, showed high levels of both MRP and MDR1 expression. None of the drug-resistant cell lines showed MRP or MDR1 **gene** amplification as judged by Southern blot analysis. U-A10 cells exhibited minimal decreased net accumulation of anthracycline, whereas U-A40 and U-A200 cells showed more significantly decreased drug accumulation as compared with U-937 cells. Subcellular anthracycline accumulation in U-937 cells as determined by fluorescence microscopy showed daunorubicin fluorescence predominately in the nucleus, However, the drug-resistant cell lines showed minimal nuclear drug accumulation with marked redistribution of drug into a vesicular compartment. Treatment with sodium azide/2-deoxyglucose. 2,4-dinitrophenol, or monensin, but not verapamil, abolished the vesicular accumulation. These studies in doxorubicin-selected U-937 cells indicate that induction of MRP overexpression occurs before that for the MDR1 **gene**. In addition, the drug-resistant cells possess an energy-dependent redistribution of anthracyclines into a nonnuclear vesicular compartment.

L33 ANSWER 13 OF 21 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 94208828 MEDLINE
DOCUMENT NUMBER: 94208828 PubMed ID: 7908888
TITLE: Features of filamentous cytoskeletons in acquired multidrug-resistance of HL-60 human leukemia cell line.
AUTHOR: Kawamura K
CORPORATE SOURCE: Third Department of Internal Medicine, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL SCIENCE,
(1994 Mar) 69 (2) 354-71.
Journal code: GA9; 17410290R. ISSN: 0367-6102.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940526
Last Updated on STN: 19970203
Entered Medline: 19940518

AB Acquired resistance to chemotherapeutic drugs by tumor cells is an important obstacle to effective therapy of human malignancy. These resistance cell lines originated from human or rodent have been characterized by increased expression of MDR (Multidrug-resistance) **gene** and P-glycoprotein which plays as efflux pump of drugs from cells. These multidrug-resistance sublines also have been reported increased activities of protein kinases and glutathione S-transferase-pi. Although there have been extensive biophysical and biochemical characterization of the differences between parental lines and MDR tumor cell sublines, morphologic observations have been limited. In this study, filamentous cytoskeletons which involve many biological phenomena such as maintenance of cell morphology, mitosis, cellular movement, transport, and adhesion, were observed by confocal laser microscopy. To compare the expression of each cytoskeletons, fluorescent intensities of cells stained for each cytoskeletons were measured by confocal laser microscopic system.

Utilizing this methodology, higher **microtubular** expression was observed in HL-60/**ADR** and K562/**ADR** than in their parental lines, but no significant differences of actin and vimentin were observed. Phosphorylation by protein kinases has been established as a key factor in the regulation of cytoskeletal function. But little is known about the role of protein phosphorylation in cytoskeletal function. Since increased activities of PKC and PTK were detected in HL-60/**ADR**, the effect of PKC inhibitor, staurosporine (STR), or PTK inhibitor, genistein (GNS), on cell growth was detected. STR and GNS reduced the resistance to **Adriamycin** in HL-60/**ADR**. Furthermore, STR and GNS disrupted the filamentous structure of **microtubules** in HL-60/**ADR**, and suppressed the expression of **microtubules** to 37%, and 49%, respectively. In contrast, PKC activator, phorbol ester (TPA), caused stronger **microtubular** assembling in HL-60/**ADR**, and increased the expression of **microtubules** to 134%. Resulting from this study, it is likely that acquired MDR of HL-60 and K562 was associated with increased expression of **microtubules**, and **microtubular** assembling or disassembling was considered to be regulated in part by PKC and PTK.

L13 ANSWER 24 OF 53 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 93219404 MEDLINE
DOCUMENT NUMBER: 93219404 PubMed ID: 8464912
TITLE: Epigenetic mechanisms of **drug resistance** : drug-induced DNA **hypermethylation** and **drug resistance**.
AUTHOR: Nyce J; Leonard S; Canupp D; Schulz S; Wong S
CORPORATE SOURCE: Department of Molecular Pharmacology and Therapeutics, School of Medicine, East Carolina University, Greenville, NC 27858.
CONTRACT NUMBER: R29 CA47217 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1993 Apr 1)** 90 (7) 2960-4.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 19970203
Entered Medline: 19930504

AB In a model system employing Chinese hamster V-79 cells, the DNA synthesis inhibitor 3'-azido-3'-deoxythymidine (BW A509U, AZT) was shown to induce genome-wide DNA **hypermethylation**, low-frequency silencing of thymidine kinase (TK; EC 2.7.1.21) gene expression, and resistance to AZT.

Twenty-four hours of exposure of V-79 cells to 150 microM AZT led to > 2-fold enhancement of genomic 5-methylcytosine levels and produced TK- epimutants at a rate approximately 43-fold above background. Such AZT-induced TK- epimutants were shown to be severely reduced in their capacity to activate AZT to its proximate antiviral form, AZT 5'-monophosphate, as compared with the TK+ parental cell line from which they were derived. TK- clones isolated under these conditions were shown to be 9- to 24-fold more resistant to the cytotoxic effects of AZT than the parental TK+ cell line and showed collateral resistance to 5-fluoro-2'-deoxyuridine. Three of four TK- epimutants could be reactivated at very high frequency (8-73%) to the TK+ AZT-sensitive phenotype by 24 hr of exposure to the demethylating agent 5-azadeoxycytidine (5-azadC), implying that drug-induced DNA **hypermethylation**, rather than classical mutation, was involved in the original gene-silencing event in these three clones. These 5-azadC-induced TK+ revertants concomitantly regained the ability to metabolize AZT to its 5'-monophosphate. RNA slot blot analyses indicated that the four AZT-induced TK- clones expressed 8.9%, 15.6%, 17.8%, and 11.1% of the parental level of TK mRNA. The three clones that were reactivatable by 5-azadC showed reexpression of TK mRNA to levels 84.4%, 51.1%, and 80.0% that of the TK+ parental cell line. These experiments show that one potential mechanism of **drug resistance** involves drug-induced DNA **hypermethylation** and resulting transcriptional inactivation of cellular genes whose products are required for drug activation.

L50 ANSWER 1 OF 2 MEDLINE
ACCESSION NUMBER: 1998422249 MEDLINE
DOCUMENT NUMBER: 98422249 PubMed ID: 9751629
TITLE: Taxol resistance mediated by transfection of the liver-specific sister gene of P-glycoprotein.
AUTHOR: Childs S; Yeh R L; Hui D; Ling V
CORPORATE SOURCE: BC Cancer Research Center, BC Cancer Agency, University of British Columbia, Vancouver, Canada.
SOURCE: CANCER RESEARCH, **(1998 Sep 15)** 58 (18) 4160-7.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981008
Last Updated on STN: 19981008
Entered Medline: 19981001

AB The sister gene of P-glycoprotein (Spgp) is a liver-specific ATP-binding cassette protein highly related to the P-glycoprotein (Pgp) family (S. Childs et al, Cancer Res., 55: 2029-2034, 1995). Spgp appears to be related to the Pgp family by an ancient duplication occurring before the division of fish and mammals. P-Glycoproteins have diverse functions including broad specificity multidrug resistance in cell lines and tumors, detoxification of tissues such as the intestine and blood-brain barrier, and phosphatidylcholine transport in liver. Spgp is a Mr approximately 170,000 glycosylated plasma membrane protein localized to the canalicular surface of hepatocytes in the rat liver. The full-length cDNA of Spgp was isolated from rat, and its expression was characterized in situ and in transfected cells. The expression of Spgp correlates with the differentiation of hepatocytes and is seen only in late liver development. It is not observed in hepatoma cell lines. The physiological function of Spgp in liver is unknown, but it maps to **2q31** in humans, in the vicinity of liver transport disorders for bile acids and cholesterol. Spgp may therefore be involved in some aspect of bile acid or cholesterol metabolism. Spgp transfectants have a low level resistance to Taxol but not to other drugs that form part of the multidrug resistance phenotype. This resistance is reversible by the Pgp-reversing agents cyclosporin A, PSC833, and verapamil, suggesting a conservation in some functions of Pgps across large evolutionary distance.

L58 ANSWER 2 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999047510 MEDLINE
DOCUMENT NUMBER: 99047510 PubMed ID: 9828229
TITLE: Up-regulation of the **multidrug resistance** genes, Mrp1 and Mdr1b, and down-regulation of the organic anion transporter, Mrp2, and the bile salt transporter, **Spgp**, in endotoxemic rat liver.
AUTHOR: Vos T A; Hooiveld G J; Koning H; Childs S; Meijer D K; Moshage H; Jansen P L; Muller M
CORPORATE SOURCE: Groningen Institute for Drug Studies, University Center for Pharmacy, University Hospital Groningen, Groningen, the Netherlands.. T.A.Vos@med.rug.nl
SOURCE: HEPATOLOGY, **(1998 Dec)** 28 (6) 1637-44.
Journal code: GBZ; 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990111

AB Endotoxin-induced cholestasis is mainly caused by an impaired canalicular secretion. Mrp2, the canalicular multispecific organic anion transporter, is strongly down-regulated in this situation, and canalicular bile salt secretion is also reduced. We hypothesized that other adenosine triphosphate-binding cassette (ABC) transporters may compensate for the decreased transport activity to protect the cell from cytokine-induced oxidative damage. Therefore, we examined the expression of ABC-transport proteins in membrane fractions of whole liver and of isolated hepatocytes of endotoxin-treated rats and performed reverse-transcriptase polymerase chain reaction (RT-PCR) on mRNA isolated from these livers. In addition, the localization of these transporters was examined using confocal scanning laser microscopy. By 6 hours after endotoxin administration, we found a clear increase of mrp1 mRNA and protein, whereas mrp2 mRNA and protein were decreased. This was confirmed in isolated hepatocytes. In addition, mdr1b mRNA was strongly increased, whereas mdr1a and mdr2 mRNA did not change significantly. Both the mRNA and protein levels of the sister of P-glycoprotein (**spgp**), the recently cloned bile salt transporter, decreased. After endotoxin treatment, the normally sharply delineated canalicular staining of mrp2 and **spgp** had changed to a fuzzy pattern, suggesting localization in a subapical compartment. We conclude that endotoxin-induced cholestasis is caused by decreased mrp2 and **spgp** levels, as well as an abnormal localization of these proteins. The simultaneous up-regulation of mrp1 and mdr1b may confer resistance to hepatocytes against cytokine-induced metabolic stress.

L58 ANSWER 3 OF 6 MEDLINE DUPLICATE 3

L36 ANSWER 31 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 94:101861 SCISEARCH
THE GENUINE ARTICLE: MU790
TITLE: NON-P-GLYCOPROTEIN MULTIDRUG-RESISTANCE IN CELL-LINES WHICH ARE DEFECTIVE IN THE CELLULAR ACCUMULATION OF DRUG
AUTHOR: CENTER M S (Reprint)
CORPORATE SOURCE: KANSAS STATE UNIV, DIV BIOL, MANHATTAN, KS, 66506 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: CYTOTECHNOLOGY, (**1993**) Vol. 12, No. 1-3, pp. 109-125.
ISSN: 0920-9069.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: AGRI
LANGUAGE: ENGLISH
REFERENCE COUNT: 91

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Non-Pgp mdr related to a defect in drug accumulation has now been documented in a number of different cell lines exposed to certain cytotoxic agents. In studies conducted thus far most isolates have been obtained after selection in either adriamycin or mitoxantrone. The work in this area is in its early stages and very little is known about the molecular events which contribute to this mode of drug resistance. At the present time no protein with drug binding properties comparable to Pgp has been identified in non-Pgp mdr isolates. Evidence based on the finding that all isolates do not respond in the same way to reversal agents such as verapamil suggests the possibility that more than one mechanism may exist for non-Pgp mdr. Future studies may thus reveal that cells contain a multiplicity of **genes** which upon transcriptional activation can function to alter drug transport processes and thus contribute to the development of mdr. Identifying and characterizing these **genes** will be important since they may function in transport systems of normal cells. The exact identity of proteins which contribute to non-Pgp mdr remains to be determined. One protein designated P190 has been found to be overexpressed in cell lines of human promyelocytic leukemia, lung and adenocarcinoma treated with adriamycin. The protein also is increased in some clinical samples from patients undergoing chemotherapy. P190 which has a minor **sequence** homology with Pgp can bind ATP and may thus contribute to the energy dependent drug efflux systems found in cells containing this protein. Transfection studies with a P190 **cDNA** should determine whether this protein actually contributes to drug resistance. Many other protein changes have been detected in non-Pgp mdr cells but the importance of these in resistance also remains to be determined. In some systems a particular protein change can be identified in multiple independent isolates suggesting a correlation between the development of resistance and the presence of this cellular alteration.

Experiments conducted thus far on the mechanism of non-Pgp mdr are intriguing. Studies utilizing fluorescence microscopy to follow the fate of daunomycin suggests that the drug passes to the interior of the cell and eventually localizes in the Golgi apparatus. Drug located at this site may move directly into an efflux pathway for rapid extrusion from the cell. Evidence also indicates that as drug leaves the Golgi some may be sequestered into other organelles such as lysosomes or mitochondria. Sequestration may thus be another means of protecting the cell from the

cytotoxic action of the drug. Very little is known of the molecular details of these events and some new technological approaches may be required to gain insight into efflux and sequestration pathways. In vitro systems for drug transport would certainly be important in these studies.

A major question to be answered in the future is whether non-Pgp mdr actually contributes to clinical drug resistance. This will certainly be clarified as new probes which can selectively detect this type of resistance are developed. Some studies have shown that in experimental isolates a low level non-Pgp mdr can precede a Pgp mdr which appears after continuous treatment of cells with drug. Possibly these findings have clinical relevance.

L42 ANSWER 22 OF 53 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 93075272 MEDLINE
DOCUMENT NUMBER: 93075272 PubMed ID: 1445391
TITLE: Detection and characterization of mRNA and proteins encoded by human rab2 low molecular weight GTP-binding protein gene.
AUTHOR: Tachibana K; Umezawa A; Takano T
CORPORATE SOURCE: Department of Microbiology, Keio University School of Medicine, Tokyo, Japan.
SOURCE: BIOCHEMISTRY INTERNATIONAL, **(1992 Oct)** 28 (1) 181-9.
Journal code: 9Y9; 8100311. ISSN: 0158-5231.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M57479; GENBANK-M86474; GENBANK-M86475; GENBANK-M86476; GENBANK-M86477; GENBANK-M86478; GENBANK-M86479; GENBANK-M86480; GENBANK-M86481; GENBANK-S48723
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 20000303
Entered Medline: 19921223

AB Three RNA species of 3.5, 2.4 and 1.4 kb were detected in all human hematopoietic, fibroblastic and tumor cell lines examined, as the mRNA of human rab2 **gene** presumably involved in **intracellular transport**. The **mRNA** differed in the length of the 3'-non-translated regions due to termination and/or processing at the alternative polyadenylation sites. The 1.4-kb rab2 RNA was predominant in Molt-4 and U-937 of mononuclear cell origin, while the 2.4-kb RNA was dominant in the other cells examined. The degradation of all rab2 RNA was similar and as slow as beta-actin RNA. The rab2 proteins were ubiquitously detected in the human cells as two phosphorylated peptides of major pp24rab2 and minor pp25rab2. pp25rab2 was slightly more phosphorylated than pp24rab2. Both rab2 proteins were abundantly detected in neural PC12 and NB3 cells, and mostly pp24rab2 was produced in the other human and rodent cells.

L18 ANSWER 2 OF 12 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97165834 MEDLINE
DOCUMENT NUMBER: 97165834 PubMed ID: 9013727
TITLE: Influence of N-methylformamide on the **intracellular transport** of **doxorubicin**.
AUTHOR: Calcabrini A; Villa A M; Molinari A; Doglia S M; Arancia G
CORPORATE SOURCE: Laboratorio di Ultrastrutture, Istituto Superiore di Sanita, Rome/Italy.
SOURCE: EUROPEAN JOURNAL OF CELL BIOLOGY, **(1997 Jan)** 72 (1) 61-9.
Journal code: EM7; 7906240. ISSN: 0171-9335.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 19970424
Entered Medline: 19970417

AB The polar solvent N-methylformamide proved to be capable of enhancing the cytotoxic potential of various antitumoral compounds, both in vitro and in vivo. In many cases, this ability depended on the sequence of treatment, and the enhancement of the cytotoxic effect occurred only when N-methylformamide administration succeeded anticancer drug treatment. The results obtained in the present study indicate that N-methylformamide interferes with the mechanisms of **intracellular transport** and efflux of the antitumoral drug **doxorubicin**. In particular, laser scanning confocal microscopy observations performed on melanoma cells (M14) after N-methylformamide administration revealed evident alterations of the microtubular network, including numerous interruptions of the microtubules. Moreover, when **doxorubicin**-treated cells were recovered in the presence of the polar solvent, the normal efflux of the anthracyclinic antibiotic appeared to be hampered, and the drug was localized mainly in well delimited perinuclear regions. Double staining experiments demonstrated the colocalization of the **doxorubicin** molecules and the WGA-stained regions as well as a close structural relationship between them and the microtubule system. These results indicate that N-methylformamide interferes with the **doxorubicin** transport inducing a damage in the microtubular network and the consequent persistence and entrapment of the drug in the regions likely occupied by the Golgi apparatus of tumor cells. This finding could account for the chemosensitizing properties exerted by N-methylformamide.

L37 ANSWER 2 OF 4 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1999:66685 SCISEARCH
THE GENUINE ARTICLE: 155UJ
TITLE: Intracellular distribution of anthracyclines in drug resistant cells
AUTHOR: Arancia G (Reprint); Calcabrini A; Meschini S; Molinari A
CORPORATE SOURCE: IST SUPER SANITA, DEPT ULTRASTRUCT, VIALE REGINA ELENA 299, I-00161 ROME, ITALY (Reprint)
COUNTRY OF AUTHOR: ITALY
SOURCE: CYTOTECHNOLOGY, (NOV-DEC 1998) Vol. 27, No. 1-3, pp. 95-111.
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
ISSN: 0920-9069.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: AGRI
LANGUAGE: English
REFERENCE COUNT: 63

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The unresponsiveness of multidrug resistant tumor cells to antineoplastic chemotherapy is often associated with reduced cellular drug accumulation accomplished by overexpressed transport molecules. Moreover, intracellular drug distribution in resistant cells appears to be remarkably different when compared to their wild type counterparts. In the present paper, we report observations on the intracellular accumulation and distribution of doxorubicin, an antitumoral agent widely employed in chemotherapy, in sensitive and resistant cultured tumor cells. The inherent fluorescence of doxorubicin allowed us to follow its fate in living cells by laser scanning confocal microscopy. This study included flow cytometric analysis of drug uptake and efflux and analysis of the presence of the well known drug transporter P-glycoprotein. Morphological, immunocytochemical and functional data evidentiated the Golgi apparatus as the preferential intracytoplasmic site of drug accumulation in resistant cells, capable of sequestering doxorubicin away from the nuclear target. Moreover, P-glycoprotein has been found located in the Golgi apparatus in drug induced resistant cells and in intrinsic resistant cells, such as melanoma cells. Thus, this organelle seems to play a pivotal role in the intracellular distribution of doxorubicin.

L42 ANSWER 6 OF 53 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 96189119 MEDLINE
DOCUMENT NUMBER: 96189119 PubMed ID: 8628304
TITLE: A yeast protein related to a mammalian Ras-binding protein,
Vps9p, is required for localization of vacuolar proteins.
AUTHOR: Burd C G; Mustol P A; Schu P V; Emr S D
CORPORATE SOURCE: Division of Cellular and Molecular Medicine and Howard Hughes Medical Institute, University of California, San Diego, La Jolla, 92093-0668, USA.
CONTRACT NUMBER: GM32703 (NIGMS)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, **(1996 May)** 16 (5) 2369-77.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U50142
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 19960708
Entered Medline: 19960621

AB In the yeast Saccharomyces cerevisiae, mutations in vacuolar protein sorting (VPS) genes result in secretion of proteins normally localized to the vacuole. Characterization of the VPS pathway has provided considerable insight into mechanisms of protein sorting and vesicle-mediated **intracellular transport**. We have **cloned** VPS9 by complementation of the vacuolar protein sorting defect of vps9 cells, characterized its gene product, and investigated its role in vacuolar protein sorting. Cells with a vps9 disruption exhibit severe vacuolar protein sorting defects and a temperature-sensitive growth defect at 38 degrees C. Electron microscopic examination of delta vps9 cells revealed the appearance of novel reticular membrane structures as well as an accumulation of 40- to 50-nm-diameter vesicles, suggesting that Vps9p may be required for the consumption of transport vesicles containing vacuolar protein precursors. A temperature-conditional allele of vps9 was constructed and used to investigate the function of Vps9p. Immediately upon shifting of temperature-conditional vps9 cells to the nonpermissive temperature, newly synthesized carboxypeptidase Y was secreted, indicating that Vps9p function is directly required in the VPS pathway. Antibodies raised against Vps9p immunoprecipitate a rare 52-kDa protein that fractionates with cytosolic proteins following cell lysis and centrifugation. Analysis of the VPS9 DNA sequence predicts that Vps9p is related to human proteins that bind Ras and negatively regulate Ras-mediated signaling. We term the related regions of Vps9p and these Ras-binding proteins a GTPase binding homology domain and suggest that it defines a family of proteins that bind monomeric GTPases. Vps9p may bind and serve as an effector of a rab GTPase, like Vps21p, required for vacuolar protein sorting.

L36 ANSWER 19 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 95:782190 SCISEARCH
THE GENUINE ARTICLE: TD887
TITLE: EXPRESSION OF MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN IN NIH/3T3 CELLS CONFERS MULTIDRUG-RESISTANCE ASSOCIATED WITH INCREASED DRUG EFFLUX AND ALTERED INTRACELLULAR DRUG DISTRIBUTION
AUTHOR: BREUNINGER L M; PAUL S; GAUGHAN K; MIKI T; CHAN A; AARONSON S A; KRUH G D (Reprint)
CORPORATE SOURCE: FOX CHASE CANC CTR, DEPT MED ONCOL, 7701 BURHOLME AVE, PHILADELPHIA, PA, 19111 (Reprint); FOX CHASE CANC CTR, DEPT MED ONCOL, PHILADELPHIA, PA, 19111; NIH, CELLULAR & MOLEC BIOL LAB, BETHESDA, MD, 20892; DERALD H RUTTENBERG CANC CTR, NEW YORK, NY, 10029
COUNTRY OF AUTHOR: USA
SOURCE: CANCER RESEARCH, (**15 NOV 1995**) Vol. 55, No. 22, pp. 5342-5347.
ISSN: 0008-5472.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 43
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Multidrug resistance is a major obstacle to cancer treatment. Using an expression **cDNA** library transfer approach to elucidating the molecular basis of non-P-glycoprotein-mediated multidrug resistance, we previously established that expression of multidrug resistance protein (MRP), an ATP-binding cassette superfamily transporter, confers multidrug resistance (G. D. Kruh et al., Cancer Res., 54: 1649-1652, 1994). In the present study, we generated NIH/3T3 MRP transfectants without using chemotherapeutic drugs to facilitate the pharmacological analysis of the MRP phenotype. MRP transfectants displayed increased resistance to several lipophilic drugs, including doxorubicin, daunorubicin, etoposide, actinomycin D, vincristine, and vinblastine. However, increased resistance was not observed for Taxol, a drug for which transfection of MDR1 confers high levels of resistance. Verapamil increased the sensitivity of MRP transfectants relative to control transfectants, but reversal was incomplete for doxorubicin and etoposide, the drugs for which MRP conferred the highest resistance levels. For the latter two drugs, MRP transfectants, which were similar to 8- and similar to 10-fold more sensitive than control cells in the absence of verapamil, exhibited 3.8- and 3.3-fold relative sensitization with 10 mu M verapamil, respectively, but remained similar to 2 and similar to 3-fold more resistant than control cells. Analysis of drug kinetics using radiolabeled daunorubicin revealed decreased accumulation and increased efflux in MRP transfectants.
Confocal microscopic analysis of intracellular daunorubicin in MRP transfectants was consistent with reduced intracellular drug concentrations, and also revealed an altered pattern of intracellular drug distribution characterized by the initial accumulation of drug in a perinuclear location, followed by the development of a punctate pattern of drug scattered throughout the cytoplasm. This pattern was suggestive of a process of drug sequestration, possibly followed by vesicle transport. Both increased drug efflux and perinuclear drug accumulation are

consistent with the reported localization of MRP in plasma and cytosolic membranes (N. Krishnamachary and M. S. Center, Cancer Res., 53: 3658-3663, 1993; hi. J. Flens et at, Cancer Res., 54: 4557-4563, 1994). These results thus indicate that the drug specificity of MRP is quite similar to that of,MDR1, but also suggest potential differences in Taxol specificity and the level of verapamil sensitivity. In addition, these results indicate that MRP functions to extrude drug from the cell, but additionally suggest the intriguing possibility that drug sequestration contributes to drug resistance by protecting cellular targets and/or contributing to drug efflux.

L36 ANSWER 16 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:188876 SCISEARCH
THE GENUINE ARTICLE: TY074
TITLE: BROAD DISTRIBUTION OF THE MULTIDRUG RESISTANCE-RELATED VAULT LUNG RESISTANCE PROTEIN IN NORMAL HUMAN TISSUES AND TUMORS
AUTHOR: IZQUIERDO M A; SCHEFFER G L; FLENS M J; GIACCONE G; BROXTERMAN H J; MEIJER C J L M; VANDERVALK P; SCHEPER R J (Reprint)
CORPORATE SOURCE: FREE UNIV AMSTERDAM HOSP, DEPT PATHOL, DE BOELELAAN 1117, 1081 HV AMSTERDAM, NETHERLANDS (Reprint); FREE UNIV AMSTERDAM HOSP, DEPT PATHOL, 1081 HV AMSTERDAM, NETHERLANDS; FREE UNIV AMSTERDAM HOSP, DEPT MED ONCOL, 1081 HV AMSTERDAM, NETHERLANDS
COUNTRY OF AUTHOR: NETHERLANDS
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (**MAR 1996**) Vol. 148, No. 3, pp. 877-887.
ISSN: 0002-9440.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 28

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Multidrug resistance (MDR) to anticancer drugs is a major cause of treatment failure in cancer. The lung resistance protein LRP is a newly described protein related to MDR in several in vitro models. LRP has been shown to be a strong predictor of poor response to chemotherapy and prognosis in acute myeloid leukemia and in ovarian carcinoma patients. Recently, based on a 57% and 88% amino acid identity with major vault proteins from Dictyostelium discoideum and Rattus norvegicus, respectively, we identified LRP as the human major vault protein the main component of highly conserved cellular organelles named vaults. We have studied the immunohistochemical expression of LRP in the freshly frozen normal human tissues and 174 cancer specimens of 28 tumor types. LRP was broadly distributed in normal and malignant cells, but distinct patterns of expression were noticed. High LRP expression was seen in bronchus, digestive tract, renal proximal tubules, keratinocytes, macrophages, and adrenal cortex, whereas varying levels were observed in other organs LRP was detected in all tumor types examined, but its frequency varied, fairly reflecting the chemosensitivity of different cancers For example, low rates of LRP positivity were seen in testicular cancer, neuroblastoma, and acute myeloid leukemia; intermediate in ovarian cancer; and high in colon, renal, and pancreatic carcinomas. The wide occurrence of LRP in normal and transformed cells in humans, its similar distribution to that of vaults in other species, as well as the high level of conservation among eukaryotic cells of both the amino acid **sequence** of the major vault protein and the composition and structure of vaults, suggest that vault function is important to eukaryotic cells.

L36 ANSWER 17 OF 42 SCISEARCH COPYRIGHT 2001 ISI (R)

L33 ANSWER 2 OF 21 CANCERLIT
ACCESSION NUMBER: 1998641039 CANCERLIT
DOCUMENT NUMBER: 98641039
TITLE: Analysis of genes that are differentially expressed in the presence of the anticancer agent 4-tert-butyl-[3-(2-chloroethyl) ureido] benzene (tBCEU) (Meeting abstract).
AUTHOR: Poyet P; Ritchot N; Potvin C; C -Gaudreault R
CORPORATE SOURCE: Departments of Biochemistry and Pharmacology, Faculty of Medicine, Laval University, Quebec, Canada, G1L 3L5.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)**. Vol. 38, pp. A4039.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199802

AB We previously showed that tBCEU is an antimitotic agent that depolymerize **microtubules**. To further investigate the mechanism of action of tBCEU, differential display **mRNA**-RT-PCR system has been used to identified **mRNA** that are either up or down regulated by the presence of tBCEU. The **mRNA** were isolated from human breast cancer MDA-MB-231 cells that was cultured in presence or in absence of 30 uM of tBCEU. The cells were incubated during 6 hours. We isolated several **mRNA sequences**, including one **sequence** that has 96,9% of homology with the **clone** 550B55 (DDBJ/EMBL/**Gene** Bank data base NID is g1579216) which is a transcript from the mitochondrial genome. This **mRNA** is up-regulated by the presence of tBCEU. This was confirmed by Northern blot analysis. We observed a maximal up-regulation after 24 hours of incubation. The effect of several antineoplastic agents such as **daunorubicin**, chlorambucil, BCNU, taxol and vinblastine was evaluated on the expression of this **mRNA**, and none of them was found to modulate its level. This indicates that it is possible to use differential display methodology to determine the mechanism of action of an antineoplastic agent. Furthermore, it might shed light a new mechanism of action that is specific for the cytotoxicity of tBCEU.

L33 ANSWER 3 OF 21 MEDLINE DUPLICATE 1

L33 ANSWER 14 OF 21 CANCERLIT
ACCESSION NUMBER: 95614979 CANCERLIT
DOCUMENT NUMBER: 95614979
TITLE: The mechanism and new approach on drug resistance of cancer cells.
AUTHOR: Miyazaki T; Takaku F; Sakurada K
CORPORATE SOURCE: Third Dept. of Internal Medicine, Hokkaido Univ. Sch. of Medicine, Sapporo 060, Japan.
SOURCE: Int Cong Ser, **(1993)**. Vol. 1026, pp. 1-335.
ISBN: 0-444-81480-9.
DOCUMENT TYPE: Book; (MONOGRAPH)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199506

AB Drug resistance has been a severe limitation on the efficacy of cancer chemotherapy, and only now are basic pharmacological and biochemical findings being applied to the problem in the clinic. This text represents the proceedings of the International Symposium on the Mechanism and New Approach on Drug Resistance of Cancer Cells, held in Sapporo, Japan, 15-17 October 1992. The 42 presentations gathered into this book cover both basic and clinical topics, but with a strong emphasis on clinical application and study results. The chapters are grouped under four major section headings: p-glycoprotein and MDR **gene**; enzyme features related with drug resistance; signal transduction related drug resistance; and overcoming drug resistance. Topics covered in the first section include the detection and expression of the human **gene** in a number of human cancer cell types, particularly leukemic cells, the activation of the **gene** by environmental stress such as ultraviolet light , serum starvation and heat shock, and isolation of the human **gene** from a library of yeast artificial chromosome **clones**. The second section deals with a range of topics including the molecular basis of resistance to the topoisomerase inhibitor CPT-11, the relation of drug resistance to glutathione content, glutathione-S-transferase activity as a determinant of resistance and its binding by drugs, **Adriamycin** resistance, cytogenetic analysis of methotrexate resistance, and cloning and characterization of thymidine phosphorylase. The third section includes presentations on the role of protein kinase C in drug resistance, expression of **microtubules** in resistant cells, resistance to **microtubule**-interactive agents taxol and the vinca alkaloids, and the roles of H-ras and neural cell adhesion molecule expression in resistance, and of myocardial beta-adrenergic receptor in aged rats. In the final section, a number of pilot clinical trials, combination studies with biological modulators, verapamil, and amphotericin B, and liposomal formulations are discussed. There is a listing of authors, but no subject index.

L33 ANSWER 16 OF 21 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 92224197 MEDLINE
DOCUMENT NUMBER: 92224197 PubMed ID: 1563018
TITLE: Selection of tumor cell variants for resistance to tumor necrosis factor also induces a form of pleiotropic drug resistance.
AUTHOR: Wright S C; Tam A W; Kumar P
CORPORATE SOURCE: Genelabs Inc., Redwood City, CA 94063.
CONTRACT NUMBER: CA 47669-01 (NCI)
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1992)** 34 (6) 399-406.
Journal code: CN3; 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920607
Last Updated on STN: 19970203
Entered Medline: 19920521

AB This study has addressed the question of whether there may be some common mechanism underlying the induction or expression of acquired cytokine and drug resistance in a tumor cell line. This study employed the tumor-necrosis-factor(TNF)-sensitive U937 tumor cell line as a model system to determine if selection of a tumor cell variant for cytokine resistance would also result in drug resistance and vice versa. Variants were selected by culturing in the presence of purified recombinant TNF or a mixed-lymphokine-containing supernatant derived from concanavalin-A-stimulated peripheral blood lymphocytes. The resulting variants were resistant not only to TNF, but also to certain chemotherapeutic drugs. The variants were most resistant to colchicine and the Vinca alkaloids, requiring drug concentrations 50- to 5000-fold higher to mediate levels of cytotoxicity comparable to that seen with the parental U937. The variants were moderately resistant to cycloheximide, actinomycin D, and mitomycin C. In contrast, these lines were relatively sensitive to **doxorubicin** or daunomycin. This phenomenon was not unique to U937 cells since we obtained a similar pattern of drug resistance by selecting TNF-resistant variants of the WEHI-164 tumor cell line. The cytokine-selected U937 variants were still lysed by NK cells, although they were somewhat less sensitive than the parental U937. Both variants were relatively resistant to lysis by activated macrophages, probably because of their TNF resistance. In an alternative selection procedure, U937 variants were derived by culturing in the presence of increasing concentrations of colchicine. The resulting variants were relatively resistant to TNF, providing further support for the existence of some common mechanism operating in induction or expression of acquired cytokine and drug resistance. The resistance mechanism apparently does not involve the P glycoprotein since the cytokine-selected U937 variants do not overexpress the mdr **gene**. This study has demonstrated that selection of TNF-resistant variants results in coexpression of a unique form of drug resistance that is characterized by resistance to **microtubule**-active drugs but not to the anthracycline antibiotics and is not associated with overexpression of the mdr **gene**.

L33 ANSWER 17 OF 21 MEDLINE DUPLICATE 8

ACCESSION NUMBER: 96080916 MEDLINE
DOCUMENT NUMBER: 96080916 PubMed ID: 7590604
TITLE: Studies on the microtubules assembly of multidrug-resistant human leukemic cells.
AUTHOR: Hara N
CORPORATE SOURCE: Third Department of Internal Medicine, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL SCIENCE, **(1995 Jul)** 70 (4) 573-89.
Journal code: GA9; 17410290R. ISSN: 0367-6102.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951208

AB The development of drug resistance in cancer cells is a significant clinical problem for the successful cancer chemotherapy. Since the cytoskeleton, including **microtubules**, may be involved in modulating cellular signal transduction, morphological and structural changes, the **microtubules** assembly of multidrug resistant cells was examined using Confocal Laser Microscope MRC500 system (Bio Rad). In this study, multidrug resistant cells were established by the continuous exposure to **ADR**(**adriamycin**) starting with 20 nM up to 1 microM. The expression of MDR-1 (multidrug resistance) **gene** was detected in K562 leukemia cells and to more extent in the multidrug resistant K562/**ADR** cells, but not in HL-60 leukemia cells and multidrug resistant HL-60/**ADR** cells by RT-PCR method. The chronological features of **microtubules** assembly in the parent cell lines were lost on day 3, after incubation with 20nM of **ADR**. In accordance with development of drug resistance, the **microtubules** assembly appeared to be more dense and stronger than that of parent cells. During the development of drug resistant cells, the **ADR**-accumulation in the nucleus was decreased according to the increase of **microtubules** assembly. In the case of incubation with 0.5 microM colcemid, an inhibitor of **microtubules** polymerization, for 3 hours, the stainings of **microtubules** were lost their fine network and appeared to be diffuse and dot-like pattern. At the same time, both untreated HL-60/**ADR** and K562/**ADR** showed the decrease of **ADR**-accumulation, but the accumulations both colcemid treated resistant cells were increased the same level of their parent cells at the point of 120 min. These results suggested that the resistance to **ADR** in human leukemia cells correlated with **microtubules** assembly, and the **microtubules** assembly played an important role of drug resistance with or without MDR-1 **gene** overexpression.

L33 ANSWER 9 OF 21 CANCERLIT

L13 ANSWER 35 OF 53 CANCERLIT
ACCESSION NUMBER: 91669635 CANCERLIT
DOCUMENT NUMBER: 91669635
TITLE: DNA STRUCTURAL ANALYSIS AND ITS RELATIONSHIP TO BIOLOGICAL FUNCTION AND MALIGNANT PROGRESSION.
AUTHOR: Norris M D
CORPORATE SOURCE: Univ. of New South Wales, Australia.
SOURCE: Diss Abstr Int [B], **(1990)**. Vol. 51, No. 5, pp. 2185.
ISSN: 0419-4217.
DOCUMENT TYPE: (THESIS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199102

AB This thesis concerns structural analysis of the mammalian genome, particularly in relationship to pediatric malignancy. The analytical procedures mark a transition from secondary to primary structure as the basis for correlations between genomic structure and biological function. Initially BD-cellulose chromatography was employed for sizing single stranded regions in otherwise double stranded DNA. Using a series of DNA hybrids, a linear relationship (R = 0.94) could be demonstrated between single stranded polynucleotide length and eluting caffeine concentration, binding to the column being independent of double stranded length. At the level of secondary DNA structure, BD-cellulose was employed to characterize intermediate stages of DNA replication, by monitoring strand length of newly synthesized polynucleotides. An array of intermediates, ranging in length to greater than 10 kb, could be discerned. Evidence was obtained for the existence of a distinct class of 10-12 kb replicative intermediates in regenerating rat liver, but not in cultured leukemic cells. The effects of S1 nuclease digestion on isolated nuclei were examined. Contrary to expectation, S1 nuclease actually promoted the formation of single stranded regions in chromatin. At the primary structural level of genomic analysis, an extended characterization of a highly **drug resistant** T-cell leukemia xenograft (LALW-2) was performed. The beta chain of the T-cell receptor gene was demonstrated to be rearranged. No amplification or rearrangement was apparent for a series of genes, including c-Ha-ras, c-fos, and c-myc, although a restriction fragment length polymorphism of the c-fms oncogene was detected. Despite having only been exposed to drugs in the course of therapy to the donor patient, cytotoxicity testing of LALW-2 cells was consistent with **multidrug resistance** (**MDR**). Lack of evidence of amplification or increased expression, for the **MDR**-associated P-glycoprotein suggested an atypical **MDR** phenotype. Also, the cells were markedly resistant to methotrexate, although such resistance could not be related to any alterations in, or amplification of the dihydrofolate reductase gene (DHFR). An investigation of the N-myc oncogene was undertaken in pediatric solid tumors and cell lines. An S1 sensitive site as located immediately 5' to the second exon of N-myc in a highly amplified and overexpressing cell line, and the site remained unchanged after induced differentiation of the cells with retinoic acid. The 5' end of N-myc was found to contain a **hypomethylated** CpG island, and this island was maintained in all tumors and tissues tested, regardless of transcriptional activity. Amplification of N-myc was detected in five cases (22%) out of a total of 23 pediatric solid tumors studied, including a three fold amplification in a primary Wilms' tumor. Gene specific analysis indicated the limitations of secondary structural analysis in providing indicators of malignant

behavior.

L13 ANSWER 36 OF 53 MEDLINE DUPLICATE 21

L13 ANSWER 21 OF 53 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 94197754 MEDLINE
DOCUMENT NUMBER: 94197754 PubMed ID: 7511899
TITLE: Regulation of folate-binding protein gene expression by DNA
methylation in methotrexate-resistant KB cells.
AUTHOR: Hsueh C T; Dolnick B J
CORPORATE SOURCE: Department of Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY 14263.
CONTRACT NUMBER: CA 09072 (NCI)
CA 16056 (NCI)
SOURCE: BIOCHEMICAL PHARMACOLOGY, **(1994 Mar 15)** 47 (6) 1019-27.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940511
Last Updated on STN: 19970203
Entered Medline: 19940505

AB Folate-binding protein (FBP) is responsible for the cellular transport of folate and methotrexate (MTX) in human KB (nasopharyngeal epidermoid carcinoma) cells. The levels of membrane-associated FBP and FBP mRNA are decreased 70-80% in an MTX-resistant KB subline (KB1BT) (Hsueh C-T and Dolnick BJ, Oncol Res 4: 497-505, 1992). Southern blot analysis did not reveal any differences in FBP gene organization or copy number between KB1BT and KB cells. However, there was a 70% decrease in the FBP gene transcription rate and no change in FBP mRNA stability in KB1BT cells. Assessing genomic DNA methylation by MspI and HpaII restriction analysis suggested that the FBP gene in KB1BT cells was more methylated than in KB cells. These alterations in the expression, transcription rate and DNA methylation state of the FBP gene did not change when KB1BT cells were grown in the absence of MTX for 8 months (MTX-free KB1BT). When MTX-free KB1BT cells were exposed to 2.5 microM 5-aza-2'-deoxycytidine for 72 hr, the FBP gene became **hypomethylated** and the levels of membrane-associated FBP and FBP mRNA increased by 2- to 3-fold. These data indicate that decreased FBP gene expression in KB1BT cells results from increased DNA methylation.

L13 ANSWER 22 OF 53 MEDLINE DUPLICATE 12

L13 ANSWER 30 OF 53 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 91161629 MEDLINE
DOCUMENT NUMBER: 91161629 PubMed ID: 2002063
TITLE: Structure of the human MDR3 gene and physical mapping of the human **MDR** locus.
AUTHOR: Lincke C R; Smit J J; van der Velde-Koerts T; Borst P
CORPORATE SOURCE: Division of Molecular Biology, The Netherlands Cancer Institute, Amsterdam.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1991 Mar 15)** 266 (8) 5303-10.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 19910505
Last Updated on STN: 19910505
Entered Medline: 19910417

AB Two genes, MDR1 and MDR3, constitute the human P-glycoprotein gene family.

To examine the evolutionary relationship between the three known classes of mammalian P-glycoprotein genes, we have cloned the MDR3 gene and compared its structure with that of the human MDR1 and the mouse mdr1 (mdr1b) genes analyzed by other groups. The MDR3 gene contains 28 exons and 27 of these contain coding sequences for the two homologous halves of the protein that correlate with functional domains. This structure is virtually identical to that of the human MDR1 gene and the mouse mdr1 (mdr1b) gene, indicating that the exon/intron structure was fixed before the duplication events that generated different classes of P-glycoproteins, but after the P-glycoproteins diverged from related genes, like the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which has an entirely different exon/intron structure. The four alternatively spliced transcripts of the MDR3 gene arise from alternative splicing of exons 23 and 26. Our analysis of DNA clones covering about 120 kilobases (kb) of the human **MDR** locus, including the entire MDR3 gene (74 kb) and the intergenic region between both genes (34 kb), combined with pulsed-field gel electrophoresis data shows that the human **MDR** locus covers about 230 kb. In contrast to the mouse **mdr** genes, both human genes are transcribed in the same direction (MDR3 located downstream of MDR1). The CpG-rich sequences marking the 5' ends of both genes are **hypomethylated** to different extents in different cell lines. **Hypomethylation** roughly correlates with transcriptional activity.

L13 ANSWER 49 OF 53 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 87191014 MEDLINE
DOCUMENT NUMBER: 87191014 PubMed ID: 3569540
TITLE: Chronic exposure to dexamethasone induces **hypomethylation** of ornithine decarboxylase genes in a human myeloma cell line.
AUTHOR: Leinonen P; Alhonen-Hongisto L; Laine R; Janne O A; Janne J
CONTRACT NUMBER: 5 RO1 CA 37695-02 (NCI)
SOURCE: FEBS LETTERS, **(1987 May 4)** 215 (1) 68-72.
Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870615

AB Chronic exposure of a human myeloma cell line to dexamethasone resulted in a selection of cells resistant to the growth-inhibitory action of the glucocorticoid. Upon acute exposure of the parental myeloma cells to dexamethasone growth inhibition was associated with depression of ornithine decarboxylase (ODC, EC 4.1.1.17) activity. However, in cells adapted to grow in the presence of micromolar concentrations of dexamethasone, ODC activity was fully comparable to that in the parental cells. Restriction enzyme analyses with the two isoschizomers HpaII and MspI as well as with the methylation-sensitive CfoI, indicated that the otherwise heavily methylated ODC gene(s) were rendered **hypomethylated** in the myeloma cells resistant to dexamethasone. This **hypomethylation** within and/or around ODC genes was associated with a 2-4-fold enhancement of accumulation of ODC mRNA.

L13 ANSWER 50 OF 53 MEDLINE

L2 ANSWER 4 OF 8 CANCERLIT
ACCESSION NUMBER: 1999700703 CANCERLIT
DOCUMENT NUMBER: 99700703
TITLE: Methylation Sensitive RDA Allows Identification of a New Transporter Gene (Rab6c) Which May Be Important in Drug Resistance (Meeting abstract).
AUTHOR: Shan J; Budman D; Yuan L; Calabro A; Vinciguerra V; Xu H-
CORPORATE SOURCE: North Shore---Long Island Jewish Health System; New York University School of Medicine, Manhasset, NY.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, (1999). Vol. 18, pp. A708.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199910

AB Drug resistance in vitro has correlated with the expression of transporter genes which act as a pump to extrude drugs from resistant cells. However, the effect of inhibition of these proteins in the clinical setting has been modest. We have explored the opposite approach, searching for genes which are expressed in chemotherapy sensitive cells but not expressed in drug resistant lines. Hence, the absence of expression of a particular gene would be associated with resistance. To accomplish this task, we have looked at differences in methylation of genes in a sensitive breast cancer line (MCF7/WT) and a resistant line (MCF7/ADR). Methylation Sensitive Representational Difference Analysis (MS-RDA) was used to isolate differentially methylated genomic fragments (DMGFs) in MCF7/ADR cells, and then these DMGFs were used to search for genes of interest. Biological function(s) of candidate genes have been studied. Employing these strategies, we have isolated several hyper-, hypomethylated, and hypomethylated/amplified DMGF. Extensive studies on a hypermethylated DMGF, **WTH3**, has led to discovery of a novel gene, Rab6c, which encodes an intracellular transporter. Northern blot and quantitative RT-PCR both demonstrated that Rab6c was expressed approximately 10, or 7 fold less respectively in MCF7/ADR cells than wild type. Over-expression of the active gene in multiple drug resistant cells partially reverses the MDR phenotype and makes such cells 3 times more sensitive to adriamycin relative to the control cells. This technique can be applied to the identification of critical genes in drug resistance in other cell lines thus leading to identification of new resistance mechanisms. In the current study, pharmacologic modulation of tumor cells to enhance expression of Rab6c may make them more sensitive to anthracyclines, while down regulation of normal cells may lead to diminished toxicity. (C) American Society of Clinical Oncology 1999.

hypermethylated MCF7/ADR

hypomethylated MCF7

L2 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:527656 BIOSIS
DOCUMENT NUMBER: PREV200000527656
TITLE: A novel gene discovered by Methylation Sensitive-Representational Difference Analysis (MS-RDA) is involved in multidrug resistance.
AUTHOR(S): Shan, Jidong (1); Yuan, Liming (1); Budman, Daniel (1); Allen, Steve (1); Chiorazzi, Nicholas (1); Vinciguerra, Vincent (1); Xu, Hao-peng (1)
CORPORATE SOURCE: (1) Molecular Oncology, Hematology/Oncology Medicine, Rheumatology/Clinical Immunology, North Shore-Long Island Jewish Health System, New York University School of Medicine, New York, NY USA
SOURCE: International Journal of Molecular Medicine, (2000) Vol. 6,
No. Supplement 1, pp. S20. print.
Meeting Info.: Joint Meeting of the 5th World Congress on Advances in Oncology and the 3rd International Symposium on
Molecular Medicine Crete, Greece October 19-21, 2000
ISSN: 1107-3756.

L2 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:468713 BIOSIS
DOCUMENT NUMBER: PREV200100468713
TITLE: A novel gene, **WTH3**, which was hypermethylated in MCF7/AdrR cells could be involved in multidrug resistance.
AUTHOR(S): Shan, Jidong (1); Yuan, Liming (1); Budman, Daniel R. (1); Allen, Steve (1); Chiorazzi, Nicholas (1); Vinciguerra, Vincent (1); Xu, Hao-peng (1)
CORPORATE SOURCE: (1) North Shore-LIJ Health System, NYU School of Medicine, Manhasset, NY USA
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (March, 2001) Vol. 42, pp. 281. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English